Obstructive Lung Disease Pharmacology

Introduction

In the last lesson, we learned about three obstructive lung diseases: bronchitis, emphysema, and asthma. We siloed these diseases in presentation and mechanism. Bronchitis is caused by chronic large-airway inflammation and excess mucus production. Emphysema is caused by septal apoptosis and the loss of surface area, pulmonary capillaries, and elastin. Asthma is defined by reversible bronchospasm initiated by IgE cross-linking of an allergen, mast cell degranulation, recruitment of eosinophils, and the activation of leukotrienes. Those are three extremely different mechanisms that you would think have three extremely different treatments.

The drugs we have to treat Asthma and COPD exacerbation overlap greatly—inhaled bronchodilators, inhaled driers of mucous secretion, and systemic corticosteroids to quell inflammation. The drugs used to treat Asthma and COPD chronically (maintenance rather than exacerbation) overlap a little, but the mechanisms of the drugs chosen to treat either one reflects the underlying pathology of that one disease.

We'll start with a discussion of the arachidonic acid pathway, and work through the medications that target that pathway, **treating inflammation**. Then we'll discuss the autonomic nervous system and the cytoplasmic second messengers that regulate the smooth muscle cells of the airway. The drugs we discuss there **treat bronchoconstriction.** We'll then move into asthma-specific treatments, including mast cell degranulation inhibitors and monoclonal antibodies. There is a brief discussion about methylxanthines before we close with a clinical glimpse, demonstrating the escalation of therapy in COPD and asthma.

Eicosanoid Pathway—Treating Inflammation

You do not need to know the steps involved in the eicosanoid pathway, aka the arachidonic acid pathway. You do need to know that there are two branches: the COX and LOX pathways.

The **COX pathway**, driven by cyclooxygenase-1 and cyclooxygenase-2, is the pathway we've seen a lot throughout the Basic Sciences. In this pathway, arachidonic acid is converted into an-intermediate-you-don't-have-to-know by COX-1 and COX-2. The outputs of the COX pathway are **prostaglandins** (protective in the kidney, protective in the gut), **prostacyclins** (responsible for the pain of inflammation), and **thromboxane A_2** (TXA_2, used in clotting). This pathway doesn't have a lot to do with obstructive lung disease, except for **aspirin-induced asthma**. Aspirin irreversibly inhibits COX enzymes, preventing the entire pathway and all its outputs. But by preventing COX, there is, in effect, more substrate (arachidonic acid) available for the LOX pathway. And as we're about to discuss, the LOX pathway is responsible for the leukotrienes that cause both inflammation (summon cells of immunity) and bronchoconstriction. Less COX activity means more LOX activity, and more LOX activity causes bronchoconstriction.

The **LOX pathway**, driven by arachidonate 5-lipoxygenase (5-LOX), is all about **leukotrienes**. In this pathway, 5-LOX takes arachidonic acid and turns it into 5-HPETE. The output of this pathway is leukotrienes, specifically **LT3, LT4,** and **LT5**. Leukotrienes induce both inflammation and bronchoconstriction. Therefore, inhibiting them will prevent or alleviate symptoms of obstructive lung disease. Inhibition of the LOX pathway comes in two forms: 5-LOX inhibitors and leukotriene receptor antagonists. Medications that inhibit 5-LOX are nonspecific because they inhibit the formation of all leukotrienes. The only 5-LOX inhibitor you should be aware of is **Zileuton.** It is an oral medication (most OLD medications are inhalers) that causes **hepatotoxicity**, so LFTs need to be monitored periodically while on it. Beyond recognizing its name, mechanism, and hepatotoxicity side effect, there isn't much more you need to know. That is because, with the advent of specific leukotriene receptor antagonists with better efficacy and no hepatotoxicity, 5-LOX inhibitors are not used much anymore.

What are used are **leukotriene receptor antagonists.** By blocking leukotriene receptors, these drugs are far more specific and have fewer side effects. There are medications that target every leukotriene receptor. The drugs commonly used in the management of asthma (and generally not used in COPD) are the LTD4 inhibitors, **montelukast** and **zafirlukast**. These medications are not nearly as effective as even the lowest-dose inhaled corticosteroids. But because they are oral and don't cause hepatotoxicity, the convenience they afford to patients makes them attractive options. They are properly used in escalation therapy and are generally used as third-line or even fourth-line drugs. They can also be used as monotherapy when the asthma is very mild and the patient wants to avoid the side effects of corticosteroids or is unwilling to use inhalers.

The mainstay of obstructive lung disease is **glucocorticoids**. Steroids inhibit both the LOX and the COX pathway as well as inhibit any cells of inflammation (so are good for asthma or COPD). Chronic administration of systemic glucocorticoids should always be avoided, as the systemic side effects are too great—hypertension, diabetes, psychosis, and avascular necrosis of the hip. But patients with obstructive lung disease derive immense value from being on chronic steroids. So, to avoid the systemic side effects but deliver steroids to the organ that needs them (the lung), medical science created **inhaled corticosteroids** (ICS). Examples are **fluticasone** and **budesonide**. Inhaled corticosteroids are hands-down the best first medication for asthma, and are used early in the management of COPD. Those that are inhaled predispose patients to develop **oral thrush**. The steroid is meant to get to the lungs. To get there, it has to go through the mouth. Proper inhalation technique, rinsing their mouth after puffing, and the use of spacers greatly reduces side effects.

When there are acute exacerbations of obstructive lung disease, a burst of systemic steroids can quell the flare. Depending on the severity, either oral (like **prednisone**) or intravenous (like **methylprednisolone**) steroids are used.

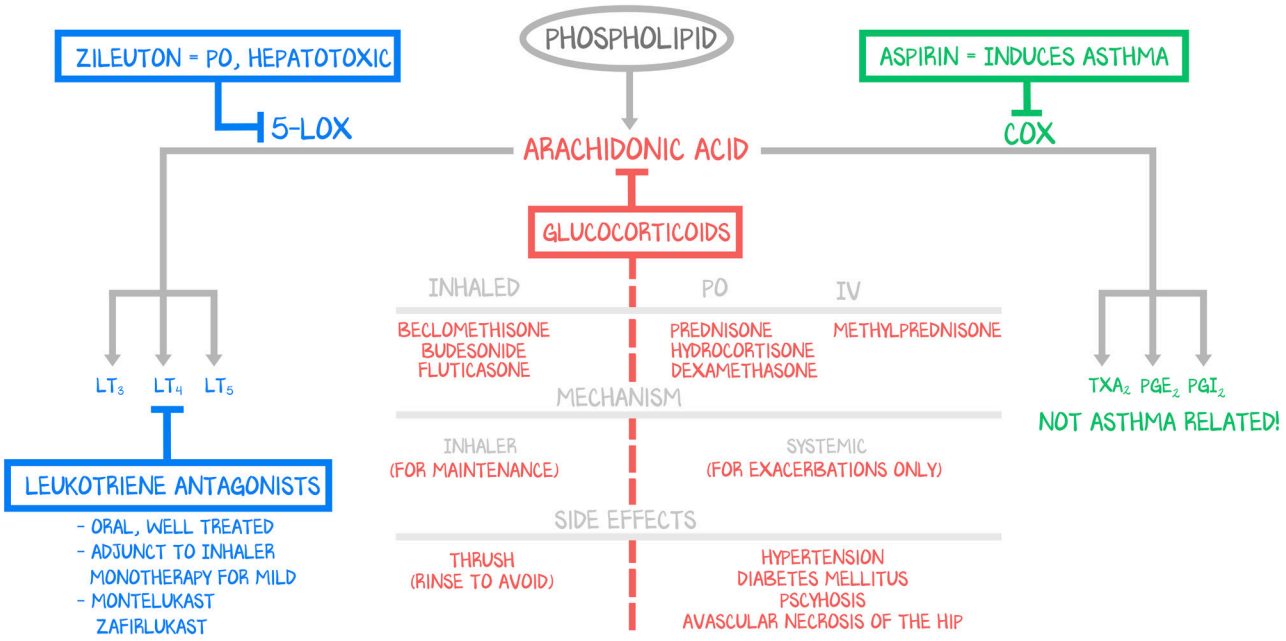

Figure 7.1: Mechanisms of Treating Inflammation
There are two branches of the arachidonic acid pathway. The COX pathway is not involved in asthma, and blocking COX enzymes may provoke an asthma attack by providing more substrate for the LOX pathway. The LOX pathway makes leukotrienes. Inhibitors of this pathway inhibit leukotriene synthesis or receptor activation. Glucocorticoids inhibit both pathways, and also have other inflammatory properties.

Smooth Muscle Tone—Bronchoconstriction

The bronchi and bronchioles have smooth muscle in their submucosa. Smooth muscle **contracts with cytoplasmic calcium** (General Physiology #15: *Smooth Muscle*). Contraction of the smooth muscle of the airway is called **bronchoconstriction**. The **M_3** muscarinic acetylcholine receptor is tethered to the **G_q-IP_3/DAG-Ca^{++}** pathway. Stimulation of the M_3 receptor increases calcium in the cytoplasm and, therefore, increases smooth muscle tone, leading to bronchoconstriction. M_3 receptors are found on the smooth muscle cells of the bronchi and bronchioles, as well as on goblet cells. There, M_3 receptor activation still works through the G_q-IP_3/DAG-Ca^{++} pathway but induces **mucus secretion**.

Inhibiting M_3 receptors prevents the calcium influx that leads to bronchoconstriction and mucus secretion, thereby leading to bronchodilation and drying up mucus membranes. There are **short-acting** muscarinic antagonists (SAMA) such as **ipratropium**. These are used for acute exacerbations. There are also **long-acting** muscarinic antagonists (LAMA) such as **tiotropium**. These are used for maintenance therapy and to prevent exacerbations. Muscarinic antagonists are not used for chronic asthma but are extremely beneficial for chronic COPD. For both asthma exacerbations and COPD exacerbations, ipratropium-albuterol inhalers are the mainstay of treatment.

Smooth muscle of the bronchi and bronchioles **relaxes** (and therefore dilates) **with cytoplasmic cAMP**. The more cAMP there is, the more dilation. The less cAMP there is, the more constriction, or rather, the less dilation. **β_2 receptors** are tethered to the G_s-AC-cAMP second messenger system. β_2 receptor stimulation leads to more cAMP and more bronchodilation. Adenylyl cyclase takes ATP and **turns it into cAMP** and, thus, bronchodilation. **Phosphodiesterase-4** (PDE-4) turns cAMP into regular AMP. Adenylyl cyclase turns on dilation. Phosphodiesterase 4 turns it off. There are also M_3 receptors on the smooth muscle cells of the bronchi and bronchioles. M_3 activates G_i, offering physiologic antagonism to β_2 receptors. There are no medications that antagonize M_3. So, although these receptors are present, they do not participate in disease or treatment.

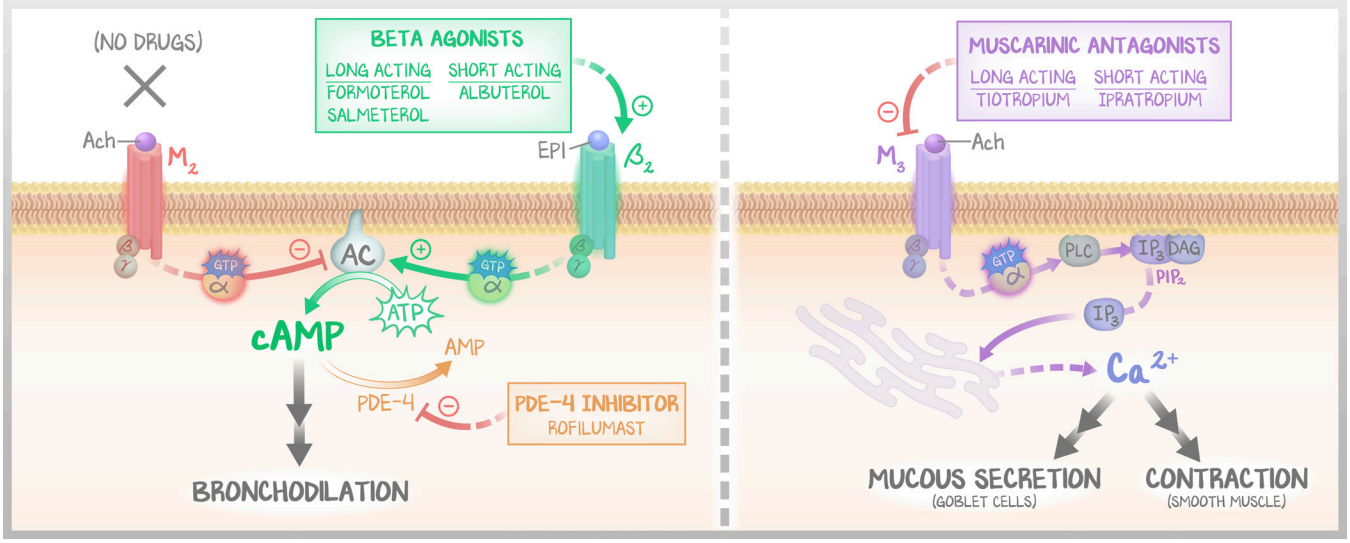

Figure 7.2: Mechanisms for Treating Bronchoconstriction
Bronchodilation is facilitated by cAMP. Adenylyl cyclase makes cAMP; phosphodiesterase degrades it. β_2 receptors stimulate adenylyl cyclase, whereas M_3 acetylcholine receptors inhibit adenylyl cyclase. Therefore, stimulation of β_2 receptors, inhibition of M_3 receptors, and inhibition of PDE-4 will all induce bronchodilation.

Stimulating β_2 stimulates adenylyl cyclase, turning on bronchodilation. There are **short-acting** β-agonists (SABA) such as **albuterol**. These are used for acute exacerbations. There are also **long-acting** β-agonists (LABA) such as **formoterol** and **salmeterol**. These are used for maintenance and prophylaxis against exacerbations. The crucial difference between COPD and asthma is that in asthma, the use of LABAs on their own without an inhaled corticosteroid **increases asthma-related death**. Always start an inhaled glucocorticoid first. In COPD, inhaled corticosteroids merely reduce hospital readmission rates, and so LABAs are sometimes used without them. Stimulating β_2 receptors elsewhere in the body leads to tremors, sinus tachycardia, and also predisposes the patient to tachyarrhythmia. Albuterol can also be used to temporize potassium in hyperkalemia-induced bradyarrhythmias. That means if someone does not already have elevated potassium, taking albuterol may cause **temporary hypokalemia**.

Inhibiting PDE-4 prevents the degradation of cAMP, leading to bronchodilation. **Roflumilast** is a phosphodiesterase-4 inhibitor and is an **oral** medication. It is not indicated in asthma; it is indicated in COPD only. PDE-4 inhibitors should be seen as the last drug added to a regimen to avoid adding oral steroids.

Asthma Only

Monoclonal antibodies against IgE. Mast cell degranulation due to IgE cross-linking initiates the early phase of asthma. Mast cell degranulation inhibitors had the right idea, but they didn't actually work very well. Recently, **omalizumab**, a monoclonal antibody against IgE, has been shown to stabilize asthma. However, because it is a monoclonal antibody—a foreign protein—it must be **infused** and can result in **anaphylaxis**. It is used in a very specific situation where a patient is maxed out on other medications, and there is evidence of elevated IgE levels, with the dose titrated to those levels. Recognize it as the IgE monoclonal antibody.

Monoclonal antibodies to IL-5. Mast cell degranulation leads to the release of IL-4, IL-5, and IL-13. IL-5 recruits eosinophils. For patients with asthma who demonstrate **peripheral eosinophilia** (there are eosinophils in the automated differential on a complete blood count), there is a good degree of suspicion that their asthma is worsened by the presence of excess eosinophils in the airway. These drugs also end in -mab, are newer, and are not yet the attention of licensing exams. So as not to confuse you, we are not putting their names in this document. There are those that target IL-5 directly and another that targets IL-5R. There are monoclonal antibodies against other implicated interleukins and their receptors as well.

Mast cell degranulation inhibition. Specific to the pathogenesis of asthma is mast cell degranulation. These medications are essentially of historical interest only. They were used for exercise-induced asthma prophylaxis. **Nedocromil** and **cromolyn** inhibit mast cell degranulation and, therefore, are supposed to prevent the onset of both the early and late phases of asthma exacerbations. It turns out they don't work that well. Because inhaled corticosteroids are so much better for maintenance and SABAs work so well for the relief of acute symptoms, these medications are no longer used in the United States. Recognize their names so that you are not tricked.

Methylxanthines

Like the mast cell degranulation inhibitors, these are of mostly historical significance in the United States. However, they continue to be used worldwide because of their low cost and convenient oral dosing. With the advent of inhaled β-agonists for acute exacerbation management and inhaled corticosteroids for maintenance therapy, methylxanthines aren't used anymore in the United States. **Theophylline** is the most common. **Caffeine** can act as a methylxanthine.

Their mechanism of action is not yet fully understood. It is believed that they work in one of two ways, or maybe both. Mechanism one: adenosine receptor antagonism. Adenosine is used to treat AVNRT (Cardiac: Electricity #4: *Arrhythmias)*. Because an increased dose of adenosine is required to break AVNRT in people who are taking theophylline, it has been proposed that these medications act on an adenosine receptor. Mechanism two: methylxanthines are effectively phosphodiesterase inhibitors. Phosphodiesterase in smooth muscle converts cAMP to ATP. cAMP induces relaxation of the smooth muscle. In blood vessels, cGMP causes arterioles to dilate, and phosphodiesterase-5 inhibitors are used for erectile dysfunction. This led to the pursuit of specific phosphodiesterase inhibitors that would affect the lung, avoid cardiac side effects, and eliminate the need for frequent monitoring of theophylline levels (it has a narrow therapeutic window and several more toxicities we're not listing for you). The research into methylxanthines discovered phosphodiesterase inhibitors. Methylxanthines are dirty drugs. And now, with such cleaner medications that we understand, we should not use methylxanthines anymore.

You may still see vignettes on licensing exams that assess theophylline and adenosine. If a patient is on theophylline, adenosine will not work. In ACLS, the training is to double the adenosine dose. Since theophylline isn't used in the United States anymore, this factoid has become essentially meaningless. However, the association still exists, and licensing exams do not change as quickly as medicine does. So, if you see a patient with supraventricular tachycardia and the patient is on theophylline, and adenosine does not work, choose theophylline as the culprit.

Clinical Glimpse

The escalation of COPD can be highly variable. We want you to learn one path only—LAMA, LABA, ICS, PDE-4. It looks something like this:

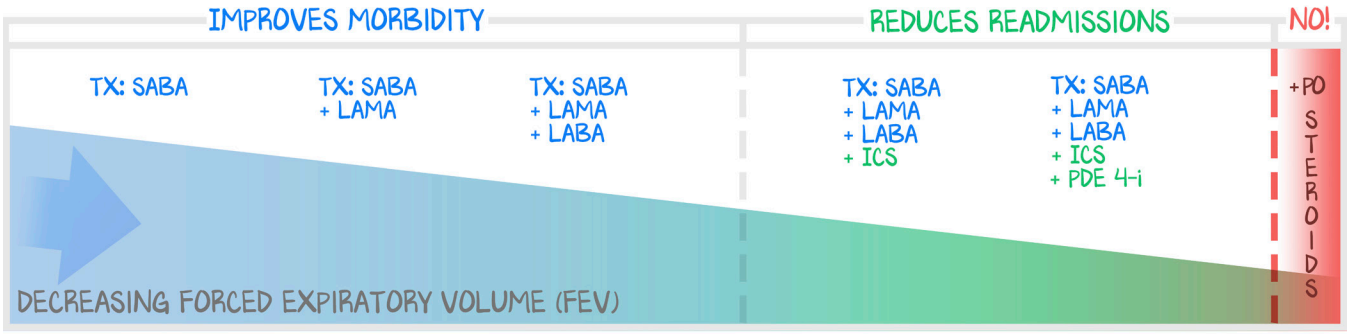

Figure 7.3: The Escalation of COPD
Treatment of COPD is based on the FEV1/FVC ratio. In mild disease, only a long-term muscarinic antagonist may be needed. As the disease burden increases, as FEV1/FVC falls, or as the patient is hospitalized, more medications are added. Long-acting β-agonists can be used on their own in COPD (but not in asthma). Inhaled corticosteroids and PDE-4 inhibitors tend only to reduce readmissions, whereas muscarinic antagonists and β-agonists improve morbidity. The only thing that improves mortality is smoking cessation.

The escalation of asthma can be highly variable. We want you to learn one path only—ICS, LABA, more ICS, even more ICS, targeted therapy. It looks something like this:

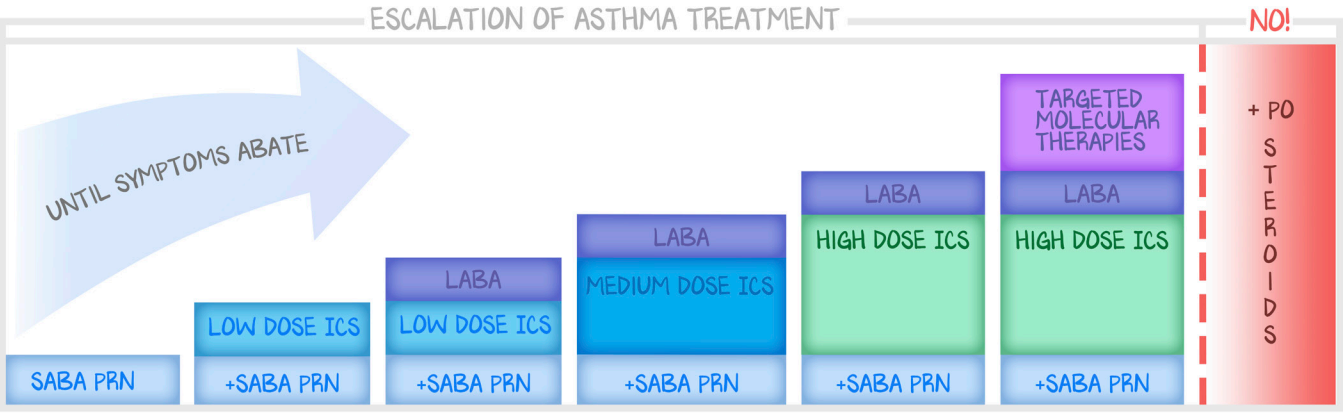

Figure 7.4: The Escalation of Asthma
Treatment of asthma involves focusing on reducing the inflammation. The backbone of asthma treatment, therefore, is inhaled corticosteroids. The emphasis of this stepwise approach is the escalation of inhaled corticosteroids with maybe the addition of a long-acting β-agonist. Oral medications, like leukotriene antagonists and 5-LOX inhibitors, can be used to augment any regimen. Finally, before oral steroids, refractory cases can try a monoclonal antibody if the patient's asthma (not just any asthma) is caused by an entity for which there is a monoclonal antibody.